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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,552	04/09/2004	Stanislav I. Svetlov	61641(49163)	1304

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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,552	SVETLOV ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Oct 13, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application Election/Restrictions

Applicant's election without traverse of Group I (claims 1-11, 15 -18) in the reply filed on October 13, 2006 is acknowledged.

Claims 1-18 are pending. Claims 12-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 13, 2006. Claims 1-11, 15-18 are under examination in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for maintaining survival of neural stem/progenitor cells isolating from postnatal 5-7 days old rat forebrains in a basal medium containing DMEM/F12, insulin, 0.8% methyl-cellulose plus 10μM LPA 18:1 (oleoyl) alone or in combination with 10ng EGF and 10ng FGF, does not reasonably provide enablement for all culture systems comprising all types of neural cells, all forms of lysophosphatidic acid (LPA) and all basal culture mediums as broadly claimed. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 1-11, 15-18 are drawn to a tissue culture system comprising at least one isolated neural cell expressing at least one LPA receptor, a LPA compound and a basal culture medium. Applicant describes that neurons isolated from postnatal day 5-7 forebrain including subependymal zone and hippocampus, which are two brain regions responsible for neurogenesis, can form neurospheres in a culture condition containing a serum-free DMEM/F12

medium, 1:1 medium supplemented with 0.8%% methyl-cellulose and insulin in the presence of 10μM LPA 18:1 (oleoyl) alone or in combination with 10ng EGF and 10ng FGF. Applicant also describes that these neurospheres express AC133, Sca-1, and LPA1-3 receptors. Both AC133 and Sca-1 are markers for the most primitive stem/progenitor cells. In addition, the neurospheres grown attached for two weeks express βIII-tubulin, which is a marker of immature neurons, and nestin, which is a marker for neural stem cells. Applicant describes that the cells induced to differentiate by attaching neurospheres to cover slips in the presence of LPA express both CNPase (an oligodendrocyte marker) and GFAP (an astrocyte marker). However, as disclosed in the specification and prior art, LPA has effects of both inducing survival and apoptosis (Ye et al. Biochem. Biophys. Acta. 2002. 1585: 108-113). LPA can induce cell proliferation and survival in oligodendrocytes, Schwann cells and astrocytes. LPA can also induce growth cone collapse and cell death in postmitotic neurons (see p.7 of the specification). In addition, different types of LPA with different lengths of carbon have different biological activities. For example, it has been shown that the mitogenic potency of oleoyel LPA is the same as palmitoyl LPA but is greater than myristoyl LPA (see p. 163, abstract, Van Corven et al. Biochem J. 1992. 281: 163-9). Thus, it is unpredictable whether different types of LPA would have the same potency. Applicant fails to provide sufficient guidance as to what other specific culture conditions are required for cells to maintain cell survival or activities as in claim 1. Although Applicant describes the range of LPA as 1μM to 50μM (see p.8 of the specification), Applicant fails to provide sufficient guidance

as to whether any range of any form of LPA other than 10 μM LPA 18:1 (oleoyl) could be used in all culture systems as recited in claim 1 since LPA has both enhancing apoptosis and survival effects on different neural cells. It has been shown that LPA is toxic to cultured hippocampal neurons derived from embryonic day 18 hippocampi (Steiner et al. Ann. New York. Acad. Sci. 2000 Apr; 905:132-41). Steiner et al. teach that treatment of rat hippocampal neurons and PC12 cells with 50μM LPA results in necrosis but low concentration of LPA 0.1μM and 1μM induces apoptosis. Thus, it is unpredictable whether all types of neurons could be treated with any concentration of LPA as in claim 1. Moreover, claim 8 recites the neural stem/progenitor cells deriving from a human. Applicant is enabled to isolate neural stem/progenitor cells from a cadaver. However, Applicant fails to provide sufficient guidance as to how to obtain live neural tissue from a live embryonic tissue or a live postnatal tissue from a human without damaging the adult brain tissue or embryos. Thus, a skilled artisan cannot contemplate how to make/use the claimed invention without further guidance and experimentation. Therefore, in view of the breath of claims, the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a tissue culture system comprising at least one isolated neural cell expressing at least one LPA receptor, a LPA compound and a basal culture medium.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 15, 17, 18 are rejected under 35 U.S.C. 102 (b) as being anticipated by US Patent No. 6150345 (issued Nov 21, 2000).

US Patent No. 6150345 teaches a tissue culture system comprising at least one isolated neural cell expressing at least one LPA receptor, a LPA and a basal medium as in claim 1 (see col. 10, lines 6-52). '345 teaches sciatic nerve isolated from postnatal day 3 rat pups and cultured in the DMEM medium (a basal medium) supplemented with 10% FCS, 20μg/ml pituitary extract, 2μM forskolin and antibiotics (see col. 9, lines 14-25). Cultured sciatic nerve cells were switched to serum free medium with or without LPA as in claim 1 (see col. 10, lines 6-52). Sciatic nerve cells express LPA receptor as evidenced in col. 11, example 4. LPA used in '345 was purchased from Avanti Polar Lipids, which is the same as in the instant application (LPA 18:1 (oleoyl) and as recited in claims 2, 3, 15, 17, 18. Thus, 1-3, 15, 17, 18 are anticipated by US Patent No. 6150345.

Claims 1-11, 15-18 are rejected under 35 U.S.C. 102 (e) as being anticipated by US2004/0014662 (published Jan 22, 2004, priority date Jul 2, 2002).

US2004/0014662 teaches a tissue culture system comprising at least one isolated neural cell expressing at least one LPA receptor, a LPA compound and a basal culture medium as in claim 1 (see p. 22, Example 3). '662 teaches culturing neural stem cells derived from anterior lateral wall of the lateral ventricles of adult mice in a neurosphere culture medium, which contains DMEM/F12, B27 supplement, HEPES and 20ng/ml EGF in the presence of as in claims 1-7, 15-18 (see p. 22, [0218], [0223],[0224]). '662 teaches that low concentration of LPA (1-10nM) stimulates adult neural stem cell proliferation (see p. 23, [0231]). LPA of '662 was purchased from the Avanti Polar Lipids Inc., which is the same as in the instant application and as recited in claims 2, 3, 17 and 18 (LPA 18:1 (oleoyl)). '662 also teaches isolating neural stem cells from a human brain or stem cells from other tissues (see p.3 [0040]). The expression of LPA receptors LPA1-3 receptors as in claims 1, 9, and 10 is an inherent feature of the neural stem cells as evidenced by Hecht et al. (J.Cell Biol. 1996. 135: 1071-1083). Hecht et al. teach that neuroblasts derived from developing cerebral cortex expressing LPA1 receptor (also named vzg-1). The expression of Sca-1/AC133 and βIII-tubulin and nestin as in claims 10 and 11 is also an inherent feature of neural stem/progenitor cells as evidenced by Locatelli et al. (J. Hematotherapy & Stem cell Res. 2003. 12: 727-734) and Hao et al. (J. Hematotherapy & Stem Cell Res.

2003. 12: 23-32). Locatelli et al. teach that neural stem/progenitor cells derived from bone marrow cultured in neurosphere culture medium express β-III tubulin and nestin and Sca-1(see p. 727, abstract). Hao et al. teaches that CD34+/CD133+ (AC133)/CD3- hematopoietic stem cells can differentiate into neural ells (see p. 23, abstract). Thus, claims 1-11 and 15-18 are anticipated by US2004/0014662.

Conclusion

NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Fukushima et al. Mol. Cell. Neurosci. 2002. 20:271-282.

Fukushima et al. Dev. Biol. 2000. 228: 6-18.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November

15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
December 6, 2006

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